The specification discloses numerous anti-angiogenic fragments other than those of the α3(IV)NC1 domain of Collagen. Applicant thus believes that the suggested change to the title may be misleading as to the full scope of the disclosure.

In addition, the compositions claimed herein are anti-angiogenic proteins and fragments, as the title indicates. Therefore Applicant respectfully disagrees that the title fails to convey the subject matter of the invention to one of ordinary skill. Applicant would be willing to amend the title to state that the proteins and fragments comprise the α1, α2 and α3 (IV)NC1 domains of Collagen and fragments and mutants thereof, but such a title might be unduly long and cumbersome.

Reconsideration and withdrawal of the objection is respectfully requested.

Abstract of the Disclosure

The Examiner has stated on page 2 of the Office Action that the abstract of the disclosure fails to include the subject matter of the instant invention, and that the abstract should give reference to fragments of the α3(IV)NC1 domain of collagen.

As stated above, the specification discloses numerous anti-angiogenic fragments other than those of the α3(IV)NC1 domain of Collagen, and although not presently claimed, they may be so in future applications. Applicant is therefore willing to amend the abstract to state that the proteins and fragments comprise the α1, α2 and α3 (IV)NC1 domains of Collagen and fragments and mutants thereof, if requested by the Examiner.

Reconsideration and withdrawal of the objection is respectfully requested.

Priority

The Examiner has stated on page 2 of the Office Action that the filing date of the claims which include the α3(IV)NC1 domain of Collagen from amino acids 54-124 and 185-203 (Claims 4 and 7, respectively) is deemed to be the filing date of the instant application.

It is unclear if the Examiner means all of the claims, that is, Claims 1-7, or only Claims 4 and 7. Clarification is requested.

The Examiner expresses the belief that "no support is found for the said polypeptide fragments in priority documents 60/126175, 60/089689 or 09/335224."

However, the Manual of Patent Examining Procedure (MPEP) states that

> (B) If the application is a continuation-in-part of an earlier U.S. application, any claims in the new application not supported by the specification and claims of the parent application have an effective filing date equal to the filing date of the new application. Any claims which are fully supported under 35 U.S.C. 112 by the earlier parent application have the effective filing date of that earlier parent application.

and that

> (D) If the application is entitled to priority under 35 U.S.C. 119(e) from a provisional application, the effective filing date is the filing date of the provisional application.

(MPEP, Version 8, § 706.02).

The Manual of Patent Examining Procedure (MPEP) discusses the standard and procedure for determining compliance with the written description requirement. It states that "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.' " (MPEP (version 8), § 2163.02, quoting *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989) The MPEP also states that "[t]he subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." (MPEP (version 8), § 2163.02).

The "Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶1, 'Written Description' Requirement" (*Federal Register*, Vol. 66, No. 4, January 5, 2001) (hereinafter, the *Guidelines*), state that regarding new claims, amended claims, or claims asserting entitlement to the benefit of an earlier priority date or filing date under 35 U.S.C. 119, 120, or 365(c):

> **The examiner has the initial burden** of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the original disclosure a description of the invention defined by the claims. . . . To comply with the written description

> requirement of 35 U.S.C. 112, ¶1, or to be entitled to an earlier priority date or filing date under 35 U.S.C. 119, 120, or 365(c), each **claim limitation must be expressly, . . . implicitly, . . . or inherently . . . supported** in the originally filed disclosure.

(at 1107, top of first column, citations omitted).

The Examiner has not met this initial burden. The Examiner has provided no evidence or reasons why a person of ordinary skill in the art would not understand anti-angiogenic fragments of an anti-angiogenic protein to include the presently-claimed subject matter. "The test is whether the originally filed specification disclosure *reasonably* conveys to a person having ordinary skill in the art that applicant had possession of the subject matter later claimed." (emphasis original, *Ex part Sorenson*, 3 U.S.P.Q.2d 1462 (Bd. U.S. Pat. No. App. & Interf. 1987)). Applicant has complied with this standard. In the present case, Applicant has discussed fragments in U.S.S.N. 60/089,689, at page 2, lines 5-27, and in Claims 7, 11, 15-16, 23, 27, 31-32, 39, 43 and 47-48. Fragments are also described in U.S.S.N. 60/126,175, at page 2, lines 3-7, page 3, lines 4-8, 11-14 and 17-20, in Example 1 (on page 26), in Fig. 1, and in Claims 5, 9 and 11. In U.S.S.N. 09/335, 224, fragments are described throughout the specification, and the examples disclose six different fragments of the full-length proteins. Anti-angiogenic fragments were therefore disclosed in all of the priority documents, and Applicant has merely pinpointed portions of the sequences described in the priority documents that have anti-angiogenic activity.

The Examiner has failed to establish a *prima facie* case for lack of written description for Applicant's claimed subject matter. As stated above, the standard for determining compliance is an objective one, and there is no literal or *in haec verba* requirement, only the need to **reasonably convey** to one of ordinary skill in the art that Applicant invented the subject matter of the claims. The Examiner has failed to present any reasons or evidence why one of ordinary skill in the art, upon reading the disclosures of U.S.S.N. 60/089,689, U.S.S.N. 60/126,175, and U.S.S.N. 09/335, 224, would not recognize that Applicant had invented the claimed subject matter, *e.g.*, fragments of α3(IV)NC1 consisting of amino acids 54-124 and 185-203 of full-length Tumstatin. Absent any such reasons or evidence, Applicant respectfully submits that support sufficient under 35 U.S.C. § 112, first paragraph has been provided, and requests that the Examiner accept a priority date of June 17, 1998 for the present application.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-3 and 5-6 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Examiner states that the claims are drawn to "a first isolated non-Goodpasture fragment of α3(IV)NC1 domain having the ability to bind the $\alpha_v\beta_3$ integrin in an RGD-independent fashion and/or the ability to inhibit proliferation of endothelial cells wherein the fragment is unable to inhibit tumor cell proliferation", and "a second isolated non-Goodpasture fragment of α3(IV)NC1 domain having the ability to bind the $\alpha_v\beta_3$ integrin in an RGD-independent fashion and/or bind endothelial cells and/or inhibit the proliferation of tumor cells and /or which is unable to inhibit the proliferation of endothelial cells". The Examiner states a belief that Applicant's disclosure is limited to fragments consisting of amino acids 54-124; amino acids 185-203; Tumstatin-N53 (amino acids 54-244); Tumstatin 333 (amino acids 1-124); Tum4 (amino acids 181-244); and SEQ ID NO:10.

As described below, however, the Examiner has failed to establish a *prima facie* case of lack of written description for the claims, and the rejection on this basis must be reconsidered and withdrawn.

Written Description Standard

As stated in the *Guidelines*, "the 'essential goal' of the description of the invention requirement is to clearly convey the information **that an applicant has invented the subject matter which is claimed**." (at 1104, quoting *In re Barker*, 599 F.2d 588, 592 n. 4, 194 U.S.P.Q. 470, 473 n. 4 (C.C.P.A. 1977), emphasis added).

The comments included with the *Guidelines* provide additional illustration of the written description analyses:

> The Guidelines indicate that there is a "strong presumption" that an adequate written description of the claimed invention is present when the application is filed, consistent with *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that **the PTO has the initial burden**

> **of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims**."). In most cases, the statement that "an originally filed claim is its own written description," is borne out because the claim language conveys to others of skill in the art that the applicant was "in possession" of what is claimed. The Guidelines emphasize that **the burden of proof is on the examiner to establish that a description as filed is not adequate and require the examiner to introduce sufficient evidence or technical reasoning to shift the burden** of going forward with contrary evidence to the applicant.

(at 1100, Comment (3), emphasis added). The Examiner has provided no evidence or reasons why persons skilled in the art would not recognize a description of the presently-claimed fragments in the prior-filed applications. The Examiner has therefore not met the Office's initial burden of proof.

The Present Rejection: Structure of the Fragments

The Examiner has failed to establish such a *prima facie* case under the *Guidelines* as described above. The only evidence or reasons that have been presented as to why a person of ordinary skill in the art, upon reading the disclosure, would not recognize that Applicant had invented the subject matter of the claims, is the Examiner's statement that

> there is no described or art-recognized correlation or relationship between the *structure* of the instant invention, an isolated non-Goodpasture fragment of α3(IV)NC1 and the *functional* ability to bind the $\alpha_v\beta_3$ integrin in an RGD-independent fashion and/or the ability to inhibit proliferation of endothelial cells wherein the fragment is unable to inhibit tumor cell proliferation.

(at page 3, emphasis original). The Examiner also states that

> in addition no described or art-recognized correlation or relationship is described between the *structure* of the instant invention, an isolated non-Goodpasture fragment of α3(IV)NC1 and the *functional* ability to bind the $\alpha_v\beta_3$ integrin in an RGD-independent fashion and/or bind endothelial cells and/or inhibit proliferation of tumor cells and /or which is unable to inhibit the proliferation of endothelial cells, upon which the invention is based.

(at page 3, emphasis original).

Applicant disagrees that the ordinarily skilled artisan would not reasonably be apprised that Applicant had possession of the claimed invention at the time of filing, and specifically traverses the rejection on that basis.

As noted by the Examiner, a "non-Goodpasture fragment" as defined in the specification (*e.g.*, at page 34, lines 12-16, and page 36, line 26 to page 37, line 2) is lacking the Goodpasture epitope, which is located within the 40 N-terminal amino acids of α3(IV)NC1. Therefore, the "structure" of such a fragment will be a fragment of SEQ ID NO:10, comprising some portion of amino acids 41-245 of SEQ ID NO:10. The sequence of a protein is its structure, and as stated on page 36, lines 15-24 of the application, it appears that secondary structure is not required for the functional abilities of the claimed molecules.

Furthermore, the specification does disclose the correlation and relationship between the structure (*i.e.*, the sequence) of these peptides and their functional activities. For instance, the specification discloses that the RGD sequence (amino acids 7-9 of SEQ ID NO:10) is not required for binding of these peptides to the $\alpha_v\beta_3$ integrin. This is surprising because the art teaches that the RGD residues are the binding site for this integrin. Therefore, contrary to the Examiner's statements, the specification does indeed describe the very correlation and relationship that the Examiner requires, and one of ordinary skill in the art therefore would envisage the genus of α3(IV)NC1 fragments other than the species disclosed.

The complete structure and function of each amino acid and fragments thereof encompassed by these claims is fully in the possession of those of ordinary skill in the art, because the specification contains all of the information necessary to create any potentially useful non-Goodpasture fragment of SEQ ID NO:10, and methods to assay each for the activity required to bring the fragment within the scope of the claims. Moreover, Applicant describes several fragments of the genus that are both non-Goodpasture fragments and inhibit endothelial cell proliferation.

Thus, it is clear that Applicant has complied with the written description requirement by both (1) having reasonably conveyed to those of ordinary skill in the art that he had invented the claimed subject matter, *i.e.*, that Applicant had possession of the claimed subject matter, and (2)

having placed the subject matter of the claims within the possession of the ordinarily skilled artisan.

In addition, the specification contains numerous working examples demonstrating the correlation and relationship between the sequence (*i.e.*, the structure) and functional activities of the claimed peptides, as well as methods of assaying additional peptides for such activities. Applicant has therefore provided teachings which guide the ordinarily skilled artisan in assessing the functional activities of any additional non-Goodpasture fragments that such an artisan may wish to make.

The Present Rejection: Representative Number of Species

The Examiner has stated on page 4 of the Office Action that Applicant has not adequately described the genus of non-Goodpasture fragments of the α3(IV)NC1 domain of collagen having specific activities. The Examiner has stated that "[t]he claimed *genus* of α3(IV)NC1 fragments may be adequately described if there is a sufficient description of a *representative number of species*." (page 4, top, emphasis original). Applicant however, has described several non-Goodpasture fragments that inhibit endothelial cell proliferation (*e.g.*, Tum1 (see, *e.g.*, page 35, lines 21-23; page 36, lines 1-3 and 15-18; Example 36), Tum2 (see, *e.g.*, page 35, lines 14-16; page 36, lines 15-18; Example 36), and amino acids 54-124 (see, *e.g.*, page 35, lines 18-20; page 36, lines 15-18)). Applicant has therefore adequately described the genus.

The Examiner has also stated that "[i]n the instant case, however, there is no described or art-recognized correlation or relationship between the *structure* of the invention, an isolated non-Goodpasture fragment of the α3(IV)NC1 and the *functional* ability". This is simply not true. As discussed above, the instant specification in fact describes precisely such a relationship, that is, the relationship between the structure, that is, the sequence of the non-Goodpasture fragments, and their disclosed functions. Applicant has also shown that these functions can be further localized to particular regions within SEQ ID NO:10. One of ordinary skill in the art would therefore understand that Applicant has disclosed the correlation between these functions and a specific structure, that is, the protein sequence.

Furthermore, Applicant has also disclosed a representative number of species by actual reduction to practice, and by reduction to drawings (*i.e.*, by disclosing the sequence).

Literal Description

The *Guidelines* also confirm that there is no requirement of literal description:

> The statutory language itself indicates that compliance with the requirements of 35 U.S.C. 112, ¶1, is judged from the standard of "any person skilled in the art." It is noted, however, that the phrases "one of skill in the art" and "one of ordinary skill in the art" appear to be synonymous. *See, e.g., Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000) ("The written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow *persons of ordinary skill in the art* to recognize that [he or she] invented what is claimed.' Thus, § 112, ¶ 1, ensures that, as of the filing date, the inventor conveyed with reasonable clarity to *those of skill in the art* that he was in possession of the subject matter of the claims." (citations omitted, emphasis added)).

(at 1103, Comment (25)).

The *Guidelines* also note that "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." (at 1106, third column). In fact, the *Guidelines* actually state that "a single species may, in some instances, provide an adequate written description of a generic claim when the description of the species would evidence to one of ordinary skill in the art that the invention includes the genus." (at 1102, Comment (16)).

Applicant respectfully submits that there is no requirement to describe every species of a claimed genus in literal terms, and that the genus presently claimed has been adequately described.

Written Description: Conclusion

The rejection on this basis must be withdrawn. The Examiner has failed to establish a *prima facie* case of lack of written description by failing to provide a preponderance of evidence or reasons why Applicant's disclosure would not reasonably convey to one of ordinary skill in

the art that Applicant invented the subject matter of the claims. Furthermore, the Examiner has failed to explain why the species disclosed fail to qualify as representative of the genus, given that Applicant has disclosed the correlation between the structure of the fragments and the functional activities of the fragments, and has also provided working examples. In the absence of such a *prima facie* case, the rejection under 35 U.S.C. § 112, first paragraph, must be withdrawn.

Claims Rejections Under 35 U.S.C. § 102(b)

Rejection in View of Kalluri et al.

Claims 1-7 are rejected under 35 U.S.C. § 102(b) as anticipated by Kalluri *et al.* (*J. Biol. Chem.* 271(15):9062-9068, 1996). The Examiner states that Kalluri *et al.* teaches an isolated non-Goodpasture fragment of α3(IV)NC1 which comprises a fragment of amino acids 54-124 and amino acids 185-203 of SEQ ID NO:10. The Examiner refers Applicant to page 9066 and Figure 4 in particular.

However, "[t]o anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art of make the anticipating subject matter." (*PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 37 U.S.P.Q.2d 1618, 1624 (Fed. Cir. 1996), citing *Chester v. Miller*, 906 F.2d 1574, 1576 n.2, 15 U.S.P.Q.2d 1333, 1336 n.2 (Fed. Cir. 1990), *In re Donohue*, 766 F.2d 531, 533, 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985)). As stated by the Federal Circuit, "[i]t is elementary that an anticipated rejection requires a showing that each limitation of a claim must be found in a single reference, practice, or device (*In re Donohue*, 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985), citing *Dalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 771, 218 U.S.P.Q. 781, 789 (Fed. Cir. 1983), *cert. denied*, 104 S.Ct. 1284, 224 U.S.P.Q. 520 (1984)).

Furthermore, a dependent claim includes all of the limitations of the claim(s) from which it depends, and in order for a prior art reference to anticipate a dependent claim, the reference *must* include all of the limitations of the dependent claim, *and* the claim from which it depends. This has been clarified by the Federal Circuit in *Atlantic Thermoplastics Co., Inc. v. Faytex Corp.* (970 F.2d 834, 23 U.S.P.Q.2d 1481 (Fed. Cir. 1992), *rehearing in banc denied*, 974 F.2d 1279, 23 U.S.P.Q.2d 1801, 974 F.2d 1299, 24 U.S.P.Q.2d 1138 (Fed. Cir. 1992)).

Applicant's claims recite fragments having specific activities. Applicant has been unable to find in Kalluri *et al.* any reference to an isolated non-Goodpasture fragment of α3(IV)NC1 that has either the ability to bind $\alpha_v\beta_3$ integrin, the ability to inhibit tumor cell proliferation, or the ability to inhibit proliferation of endothelial cells. In addition, Applicant has amended Claims 1-3 to recite a composition comprising an isolated non-Goodpasture fragment of α3 NC1 domain of Type IV collagen, and Claim 4 recites a composition not disclosed in Kalluri *et al.* The reference fails to disclose all of the elements of the rejected claims, and therefore fails to anticipate Applicant's claims. Applicant respectfully requests that the rejection on this basis be reconsidered and withdrawn.

Rejection in View of Han et al.

Claims 5-7 are rejected under 35 U.S.C. § 102(b) as anticipated by Han *et al.* (*J. Biol. Chem.* 272(33):20395-20401, 1997). The Examiner states that Han *et al.* teaches an isolated non-Goodpasture fragment of α3(IV)NC1 which comprises fragment of amino acids 54-124 and amino acids 185-203 of SEQ ID NO:10. The Examiner refers Applicant to the abstract in particular.

Applicant respectfully disagrees, but has canceled Claims 5-7 in the interests of expediting prosecution. The rejection is therefore moot, and Applicant respectfully requests that it be reconsidered and withdrawn.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If

the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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Concord, MA 01742-9133
Dated: December 4, 2001

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 103, lines 16 through 22 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

For the renal cell carcinoma cell model, 2 million 786-O cells were injected subcutaneously into 7- to 9-week-old male athymic nude mice. The tumors were allowed to grow to either about 100 mm^3 or about 700 mm^3. Each group contained 6 mice. Canstatin in sterile PBS was injected I.P. daily at a concentration of 10 mg/kg for 10 days. The control group received the same volume of PBS. The results are shown in Figs. 17C (100 mm^3 tumors) and 17D[15D] (700 mm^3 tumors). In both groups, the Canstatin-treated (■) tumors actually shrank relative to the controls (□).

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A composition comprising an [An] isolated non-Goodpasture fragment of α3(IV) NC1 domain, having one or both of the following characteristics selected from the group consisting of:

   (a) the ability to bind $\alpha_V\beta_3$ integrin; and

   (b) the ability to inhibit proliferation of endothelial cells; and

   a pharmaceutically-acceptable carrier.

2. (Amended) The composition [isolated fragment] of Claim 1, wherein the ability to bind $\alpha_V\beta_3$ integrin is RGD-independent.

3. (Amended) The composition [isolated fragment] of Claim 2, further comprising the inability to inhibit tumor cell proliferation.

4. (Amended) An [The] isolated fragment of α3(IV) NC1 domain [Claim 3], having the amino acid sequence of amino acid residue 54 to amino acid 124 of SEQ ID NO:10.